N.A., TIPS 18 : Suppl 1, 1997, 77-84

Ca^{2+} channels

Nomenclature	L	N	P	Q	T
Current	I_L	I_N	I_P	I_Q	I_T
Conductance*	25 pS	12–20 pS	9,14,19 pS	–	8 pS
Agonist ligands	(–)-(s)-BayK8644† SZ(+)-(s)-202-791†	–	–	–	–
Blockers	nifedipine diltiazem verapamil	ω-conotoxin GVIA	ω-agatoxin IVA (IC_{50}~1 nM)[1] ω-conotoxin MVIIC¶ ω-agatoxin IIIA¶	ω-agatoxin IVA (IC_{50}~90 nM)[1]~ ω-conotoxin MVIIC§	Ni^{2+}§ octanol§ flunarizine§
Regulation	high-voltage activated slow inactivation¥ PKA-modulated	high-voltage activated moderate rate of inactivation‡¥	moderate-voltage activated non-inactivating	high-voltage activated	low-voltage activated fast inactivation
Structural information#	α1S, α2–δ, β, γ α1C, α2–δ, β α1D, α2–δ, β	α1B, α2–δ, β	α1A? + accessory subunits	α1A? + accessory subunits	unknown

*conductance measured with ~100 mM Ba^{2+} as charge carrier

†enhance the probability of mode-2 (long duration) openings of the channel; particularly effective at negative voltages

§nonselective block

¶both compounds can also block N channels[2–5]; ω-agatoxin IIIA can additionally block L channels[4,5]

¥rate of inactivation may be greatly accelerated by $[Ca]_i$

‡N channels show transitions between inactivating and non-activating states

#predominant distribution of α-subunits: α1S, skeletal muscle; α1C, cardiac and smooth muscle, brain; α1D, endocrine, kidney, brain; assignment of the α1A subunit to the kinetically and pharmacologically defined P and Q channel types is uncertain

Comment: An R-type channel which is resistant to all established organic and peptide Ca^{2+} channel ligands has been proposed[6]. I_R is reported to be blocked by low concentrations of Ni^{2+} (IC_{50} ~50 μM).

contd ....

Structural information: Ca^{2+} channels form hetero-oligomeric complexes. The α1 subunit is pore-forming and provides the extracellular binding site(s) for agonists and antagonists. The α1 subunit belongs to a heterogeneous family. Six α-subunits have been cloned (α1S, α1A, α1B, α1C, α1D and α1E) of 1610–2424 amino acid length. Each subunit has four homologous repeats (I–IV), each having six transmembrane domains (TMs). Gating is thought to be associated with the membrane spanning S4 segment which contains highly conserved positive charges. All α-subunit genes give rise to alternatively spliced products. Multiple isoforms of the β-subunit exist (β1, β2, β3 and β4) as polypeptides of 477–632 amino acids. There are three alternatively spliced forms of β1 (β1a, β1b and β1c). The β-subunits lack potential *N*-linked glycosylation sites, suggesting that they do not transverse the membrane. α2- and δ-subunits exist as two disulphide linked polypeptides, the α2- and δ-subunits probably possess two and one transmembrane domains, respectively. The γ-subunit, which appears to be confined to skeletal muscle, consists of 222 amino acids and has four TMs.

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Chemical names

- **SZ(+)-(s)-202-791:** isopropyl 4-(2,1,3-benzoxadiazol-4-yl)-1,4-dihydro-2,6-dimethyl-5-nitro-3-pyridinecarboxylate
- **(–)-(s)-BayK8644:** (–)-(s)-methyl-1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluromethylphenyl)-pyridine-5-carboxylate

K^+ channels (voltage-sensitive)

Nomenclature	K_A	K_V	$K_{V(r)}$	$K_{V(s)}$	K_{SR}
Other names	A-channel	delayed rectifier	rapid delayed rectifier	slow delayed rectifier	sarcoplasmic reticulum channel
Current	$I_{K(A)}$	$I_{K(V)}$	$I_{K(Vr)}$	$I_{K(Vs)}$	$I_{K(SR)}$
Conductance	< 1–20 pS	–	–	–	180 pS
Openers	–	–	–	–	–
Blockers	4-AP quinidine tetrahydroaminoacridine mast-cell degranulating peptide phencyclidine dendrotoxins[†]	4-AP dendrotoxins[†] phencyclidine phalloidin 9-aminoacridine margatoxin imperator toxin charybdotoxin	dofetilide sotalol UK66914 E4031 quinidine tedisamil	LY97241	decamethonium hexamethonium Cs^+
Regulation	rapid activation and inactivation	delayed activation slow inactivation	rapid activation and inactivation	very slow activation and inactivation	strong voltage sensitivity low K^+/Na^+ selectivity
Structural information	tetramer of α-subunits (each 6TM); intracellular β-subunits which may confer rapid inactivation have been identified	tetramer of α-subunits (each 6TM)	tetramer of α-subunits (each 6TM); probably products of the human *ether-à-go-go*-related gene (HERG)[‡]	unknown	unknown

[†]there are a variety of dendrotoxins; selectivity at different channels can be determined at different concentrations

K^+ channels (Ca^{2+}-sensitive)

Nomenclature	BK_{Ca}	IK_{Ca}	SK_{Ca}
Other names	high conductance Ca^{2+}-sensitive K^+ channel	intermediate conductance Ca^{2+}-sensitive K^+ channel	small conductance Ca^{2+}-sensitive K^+ channel
Current	$I_{BK(Ca)}$	$I_{IK(Ca)}$	$I_{SK(Ca)}$
Conductance	100–250 pS	18–50 pS	6–14 pS
Openers	NS004 NS1619 DHS-1	–	–
Blockers	iberiotoxin (+)-tubocurarine charybdotoxin noxiustoxin penitrem-A TEA	cetiedil trifluoroperazine haloperidol	apamin leiurotoxin 1 (+)-tubocurarine
Regulation	voltage-sensitive	voltage-sensitive	little or no voltage-sensitivity
Structural information	tetramer of α-subunits (each 6TM); additional membrane-spanning β-subunits which may modify voltage-sensitivity have been identified	unknown	tetramer of α-subunits (each 6TM); voltage-sensor (S4) region is poorly charged

K^+ channels (receptor-coupled)

Nomenclature	K_M	K_{ACh}
Other names	muscarinic-inactivated	atrial muscarinic-activated
Current	$I_{K(M)}$	$I_{K(ACh)}$
Conductance	5–18 pS	7–50 pS
Openers	somatostatin β-adrenoceptor agonists (receptor-coupled)	–
Blockers	Ba^{2+} bradykinin (receptor-coupled)	Ba^{2+} Cs^+ 4-AP TEA quinine
Regulation	time-dependent and voltage-sensitive slow activation non-inactivating non-rectifying	voltage-sensitive inwardly rectifying
Structural information	unknown	probably a tetramer of the products of the genes Kir3.1 and Kir3.4

contd —

Nomenclature	K_{IR}	K_{ATP}	K_{Na}	K_{Vol}
Other names	inward rectifier	ATP-sensitive	Na^+-activated	cell-volume sensitive
Current	$I_{K(IR)}$	$I_{K(ATP)}$	$I_{K(Na)}$	$I_{K(Vol)}$
Conductance	5–30 pS	5–90 pS	170–210 pS	16–40 pS
Openers	–	levcromakalim diazoxide aprikalim pinacidil	–	–
Blockers	LY97241 gaboon viper venom Sr^{2+} Ba^{2+} Cs^+	glibenclamide tolbutamide phentolamine ciclazindol lidocaine	Mg^{2+} Ba^{2+}	quinidine lidocaine cetiedil
Regulation	Mg^{2+} and intracellular polyamines responsible for inward rectification	ATP-inhibited nucleoside diphosphate-facilitated inwardly rectifying pH-sensitive	voltage-insensitive	activated by increased cell volume
Structural information	tetramer of α-subunits (each 2TM)	tetramer of α-subunits (each 2TM); ATP and (?) opener sensitivity associated with the β-subunits (sulphonylurea receptor)		

contd –

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Chemical names

- **4-AP:** 4-aminopyridine
- **DHS-1:** dehydrosoyasaponin-1
- **E4031:** 1-(2-(6-methyl-2-pyridyl)ethyl)-4-(4-methylsulphonyl aminobenzoyl)piperidine
- **LY97241:** *N*-ethyl-*N*-heptyl-4-nitrobenzenebutanamine ethanedoic acid
- **NS104:** 1-(2-hydroxy-5-chlorophenyl)-5-trifluromethyl-2-benzimidazolone
- **NS1619:** 1-(2′-hydroxy-5′-trifluromethylphenyl)-5-trifluro-methyl-2(3*H*)benzimidazolone
- **TEA:** tetraethylammonium
- **UK66914:** (*N*-(1-(1-hydroxy-2-[4-pyridinyl)-1-piperazinyl]ethyl)phenyl)methanesulphonamide

Na^+ channels

Nomenclature*	I	II†	III	μ1	H1	PN3[4,5]
Conductance	–	20 pS	16 pS	–	–	–
Openers	–	–	–	–	–	–
Blockers	tetrodotoxin saxitoxin	tetrodotoxin saxitoxin	tetrodotoxin saxitoxin	tetrodotoxin μ-conotoxins GIIIA, GIIIB, GIIIC	tetrodotoxin (high concentrations)†† saxitoxin (high concentrations)	tetrodotoxin resistant‡‡
Regulation§	–	V_{50}—41 mV V_h—64 mV	V_{50}—10 mV V_h—40 mV	V_h—67 mV	–	V_h—30 mV
Structural information¶	2009 aa	2005 aa	1951 aa	1840 aa	2018 aa	1957[4]/1956[5] aa

*there is no official recommendation regarding the classification of sodium channels. Functional sodium channels that have been identified in the rat or mouse are listed

†a sequence variant, termed IIA, with similar or identical properties results from alternative splicing

§V_{50}, voltage required for half-maximal activation; V_h, voltage required for half-maximal inactivation

¶a single α-subunit is sufficient to encode a functional channel; the number of amino acids comprising each α-subunit is given. Although some brain sodium channels are associated with β1- and β2-subunits *in vivo*; it is uncertain whether all three brain types (i.e. I, II and III) associate with accessory proteins. The skeletal muscle μ1-subunit probably associates with a β1-subunit. The human homologues of the rat II[1], μ1[2] and H1[3] channels have been cloned and functionally expressed

††block occurs only with micromolar concentrations of TTX. H1 is generally classed as TTX resistant

‡‡TTX resistant (IC_{50} ~60 μM)[6], has properties similar to a population of TTX resistant Na channels endogenous to rat small dorsal root ganglion neurones[6]

Comments: The channels listed are predominantly expressed in: brain (I, II and III); adult skeletal muscle (μ1); heart and denervated skeletal muscle (H1), and dorsal root and trigeminal ganglion neurones (PN3). In addition to the channels listed, novel partial cDNA clones have been isolated for channels termed rat 6 (neurones and glia)[7], PN1 (dorsal root ganglia – predicted TTX sensitive; unpublished), Na-G (glia)[8] and $hNa_v2.3$ (heart)[9].

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